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A Phase I Trial of Dose Dense (Biweekly) Carboplatin Combined with Paclitaxel and Pegfilgrastim: A Feasibility Study in Patients with Untreated Stage III and IV Ovarian, Tubal or Primary Peritoneal Cancer: A Gynecologic Oncology Group Study

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Abstract

Purpose—Dose-dense regimens have been shown to improve outcome when given as adjuvant therapy to patients with breast cancer compared with their three weekly counterparts. We investigated the feasibility of a dose-dense regimen with carboplatin/paclitaxel followed by pegfilgrastim in patients with advanced ovarian cancer. We also investigated the toxicities including the percentage of patients with grade 2 or greater peripheral neurotoxicity and the clinical response of this regimen.

Patients and Methods—Women with untreated Stage III or IV epithelial ovarian, (fallopian) tubal, or primary peritoneal cancer were treated with carboplatin area under the curve (AUC) 5 and paclitaxel 175 mg/m² day one, and pegfilgrastim 6 mg day two every two weeks for six cycles.

Results—Between 9/06 and 9/08, 43 patients enrolled. Thirty one patients completed six or more cycles of therapy. The dose limiting toxicities resulting in treatment discontinuation included: grade 3 and 4 neuropathy, grade 4 thrombocytopenia, grade 4 thrombocytopenia/grade 3 febrile

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CONFLICT OF INTEREST

The co-authors wish to report that there are no conflicts of interest, with the exception of Dr. Ron Swenson who has stock ownership in Amgen and has an Investigator initiated research grant with Genzyme, Bayer, and Abraxis Oncology.

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neutropenia, and grade 4 supraventricular tachycardia. Twelve patients (30%) had $\geq$ grade 2 neuropathy from this regimen. The overall response rate in patients with measurable disease was 58% (11 out of 19).

Conclusion—Dose dense carboplatin/paclitaxel appears to be effective. However, based on dose limiting toxicities occurring when administering 6 cycles of treatment, it is not feasible. Given the neuropathy and thrombocytopenia, we do not recommend 6 cycles of this regimen without modification.

Keywords

chemotherapy; dose dense; ovarian cancer

INTRODUCTION

Ovarian cancer is the leading cause of death from gynecologic cancers in the western world. It is estimated that about 21,550 women in the U.S. will be diagnosed with, and 14,600 women will die of ovarian cancer in 2009. [1] At the time of diagnosis, more than 75% of patients with ovarian cancer present with advanced disease. [2] The current standard of care for advanced ovarian cancer is carboplatin and paclitaxel therapy given every three weeks. [2,3] Despite improvements in response rates (RR) and progression free survival (PFS), the overall survival (OS) with this standard is still disappointing with median OS of 43.3 months. [3] Several studies done during the 1990's in breast and ovarian cancer have demonstrated that increasing the dose of drugs beyond standard dosing (at the same dosing interval) was not beneficial and added toxicity. [4–8] However, dose intensity may also be increased by shortening the cycle interval while the dose per cycle and overall dose remain the same. [9,10] This approach has been tested in breast cancer. Citron et al. have shown that dose dense (biweekly) regimens when given with growth factor support, improve PFS (26% reduction in relapse) and OS (31% reduction in mortality) without significantly more toxicity when given as adjuvant therapy to breast cancer patients in comparison with their three weekly counterparts. [10] Based on these findings, dose dense doxorubicin/cyclophosphamide followed by paclitaxel was widely adopted for adjuvant chemotherapy for breast cancer.

Potential advantages for dose dense therapy in ovarian cancer include shortening of the overall time of administration of chemotherapy, possibly enhanced anti angiogenesis effects of paclitaxel, and greater probability of exposure to paclitaxel during cell division and lessening chances of repairing sub-lethal platinum-induced DNA damage. Several previous studies have addressed dose dense chemotherapy in recurrent ovarian cancer. All of these trials were confined to previously treated patients and employed weekly regimens. [11–14] Although there were variations in dose and schedule as outlined in Table 1.

More recently, Katsumata et al. reported the first large randomized study addressing dose dense therapy as front line treatment for patients with advanced ovarian cancer. Six hundred thirty seven patients were randomized to carboplatin area under the curve (AUC) 6 with paclitaxel 180 mg/m² day one every three weeks or paclitaxel 80 mg/m² day one, eight, 15 every three weeks for six cycles. [15] Both PFS (28 months versus 17 months, $p=0.0015$) and OS at three years (72% versus 65%, $p=0.03$) were superior for the dose dense arm as compared with the conventional arm. Although grade 3 and grade 4 anemia was more common in the dose dense arm, other toxicities were similar in both groups.

Based on the survival benefit seen with biweekly therapy in breast cancer and the encouraging tolerance and results of dose dense therapy in previously treated ovarian cancer, we proposed to study biweekly paclitaxel 175 mg/m² in combination with carboplatin AUC

5 with pegfilgrastim to evaluate the feasibility of this dose dense regimen given for six cycles. We sought to deliver such treatment without grade 3 or worse non hematologic toxicities, and without major dose delays or additional hematologic support (red cell or platelet transfusions, or admissions for febrile neutropenia) in untreated patients with advanced ovarian cancer. The toxicity of this regimen using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 with special attention to grade 2 or greater peripheral neuropathy and the probability of response in patients with measurable disease were secondary objectives.

PATIENTS AND METHODS

Eligible patients had a diagnosis of previously untreated Stage III or IV primary peritoneal, fallopian tube, or epithelial ovarian carcinoma. Patients had to have adequate bone marrow function (absolute neutrophil count [ANC] $\geq 1500/\text{mm}^3$ and platelets $\geq 100,000/\text{mm}^3$), renal function (serum creatinine $\leq 1.5 \times$ upper limit of normal [ULN]), hepatic function (bilirubin $\leq 1.5 \times$ ULN, AST/Alkaline Phosphatase $\leq 2.5 \times$ ULN), neurologic function (sensory and motor neuropathy $\leq$ CTCAE v3.0 grade 1), and Gynecologic Oncology Group-performance status (GOG-PS ≤ 2). Patients must have had appropriate surgery and signed an approved informed consent for study participation. The study received approval from the institutional review board of each participating institution.

Treatment consisted of carboplatin AUC 5 intravenously followed by paclitaxel 175 mg/m^2 intravenously over three hours on day one of every 2 week cycle for 6 cycles. On day two, patients were given pegfilgrastim 6 mg subcutaneously. At the discretion of the treating physician, patients were eligible to receive an additional two cycles of therapy (eight cycles total), if they were responding to and tolerating therapy. The initial dose of carboplatin was calculated according to the Calvert equation, by equating glomerular filtration rate (GFR) to the creatinine clearance (Ccr), from the Jelliffe formula. [16,17] In the absence of new renal obstruction or other renal toxicity greater than or equal to CTCAE grade 2 (serum creatinine $>1.5 \times$ ULN), the dose of carboplatin was not recalculated for subsequent cycles.

Dose limiting toxicities (DLT) were defined as febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an ANC $< 1000/\text{mm}^3$ and fever $\geq 38.5^\circ\text{C}$), grade 4 neutropenia ($<500/\text{mm}^3$) lasting $\geq$ seven days, grade 4 thrombocytopenia ($<25,000/\text{mm}^3$), grade 3 thrombocytopenia (25,000 to $<50,000/\text{mm}^3$) with bleeding, dose delay $>$ two weeks, grade 3 or 4 non hematologic toxicities (excluding fatigue, hypersensitivity reaction, nausea and vomiting, constipation or bone pain), and any treatment related death. Paclitaxel hypersensitivity was not a DLT and patients experiencing this toxicity were replaced. Treatment decisions were based on the ANC and platelet count, with subsequent cycles of therapy administered only after the ANC $\geq 1000/\text{mm}^3$ and the platelet count $\geq 75,000/\text{mm}^3$. Therapy was delayed for a maximum of two weeks until those values were achieved. Patients who failed to recover adequate counts within a two week delay no longer received protocol directed chemotherapy. There were no modifications for uncomplicated grade 4 neutropenia lasting $<$ seven days or uncomplicated grade 3 thrombocytopenia. For febrile neutropenia, grade 4 neutropenia lasting $\geq$ seven days, grade 4 thrombocytopenia, or grade 3 thrombocytopenia with bleeding, the carboplatin dose was reduced one level to AUC 4. For the same complications at AUC 4, the patient was taken off study. If there was a delay on the basis of thrombocytopenia or neutropenia of 1–14 days, in the absence of DLT, the AUC was lowered to 4. For any delay greater than 14 days, the patient was taken off the study regimen. Grade 2 or greater peripheral neuropathy or grade 3 or greater elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or bilirubin required dose reduction of one level for paclitaxel to 135 mg/m^2 and delay in subsequent therapy for a maximum of two weeks until recovered to

grade 1. For the same complications at 135 mg/m², the paclitaxel dose was reduced to 110 mg/m² again with delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1.

Patients who completed four or more cycles of chemotherapy were assessed for response. Patients who had target lesions on baseline computerized tomography (CT) scans were categorized as measurable. Patients who had non target lesions on baseline CT scan or abnormal CA 125 prior to beginning chemotherapy were considered evaluable. Patients who had normal pre-chemotherapy CT scans and normal pre-chemotherapy CA 125 levels were categorized as inevaluable for response. CT scan was performed at baseline, at completion of chemotherapy, and again at four to 12 weeks after the last treatment and evaluated by Response Evaluation Criteria in Solid Tumors (RECIST). [18] Serum CA 125 level was evaluated every four weeks during treatment. In patients with non-measurable disease, complete response by CA 125 was defined as return of serum CA 125 levels to normal values for at least four weeks, partial response as >50% decrease in serum CA 125 levels, and increasing disease as a doubling from either the ULN or nadir CA 125, within 8 weeks of study entry.

All patients were followed until disease progression, study therapy completion, or withdrawal. After the completion of study therapy, all patients were monitored for delayed toxicity and survival for a period of one year.

The study utilized a two stage group sequential design with dose limiting toxicities in six cycles to determine regimen feasibility. Twenty patients were entered into each stage. If no more than four DLT occurred in the first stage, the trial would have been stopped and the regimen would be considered feasible for phase III investigation. If there were between five and seven DLT during the first stage, the regimen would be considered feasible enough to warrant further investigation in a second stage. If eight or more DLT occurred in the first stage, the regimen would be considered not feasible. If 12 or more DLT (cumulatively) occurred following accrual of a total of 40 patients the regimen would be considered not feasible. If 11 or fewer events occurred after accrual of 40 patients, the regimen would be considered feasible for phase III investigation.

Regimens with a true probability of inducing a DLT in 6 cycles equal to 40% or more are considered not feasible for administration while regimens with a true probability equal to 20% or less are considered tolerable for administration. If the regimen is truly tolerable, then the group sequential decision rules will correctly declare the regimen as being feasible with at least 91% probability. On the other hand, if the regimen is truly not feasible, then the decision rules will declare the regimen as such with at least 91% probability.

RESULTS

Forty-three patients were enrolled between September 2006 and September 2008. Characteristics of these 43 patients are outlined in Table 2. The mean number of cycles delivered to patients was 5.4 (median 6; range 0–8). Thirty-one patients (72%) completed six or more cycles of therapy (Table 3). Two patients who did not complete a cycle of therapy had paclitaxel hypersensitivity reactions.

In the first stage of accrual, twenty-two patients were enrolled and fifteen patients completed 6 cycles of therapy. One patient discontinued for disease progression after 2 cycles (later found to be gastric primary), one due to hypersensitivity reaction to paclitaxel during cycle 1, and one due to fatigue post cycle 1. The other 4 patients were discontinued due to DLT. There were 6 DLT related to chemotherapy: 1 grade 3 dehydration, 1 grade 3 and 1 grade 4 neuropathy, 1 grade 4 thrombocytopenia at carboplatin AUC 4 (–1 dose level), 1 grade 4

supraventricular tachycardia (SVT), 1 grade 3 non-neutropenic pneumonia. Since there were over 4 DLT but less than 8 DLT, the study was considered feasible to warrant further evaluation. In the second stage of accrual, twenty-one patients were enrolled and sixteen completed 6 cycles of therapy. One patient discontinued treatment due to a severe hypersensitivity reaction to paclitaxel at cycle 1, one due to an intraperitoneal abscess after 5 cycles, and another due to sudden death which was not felt to be treatment-related after 3 cycles. The other 2 patients discontinued treatment due to DLT including one due to treatment delay greater than 14 days for febrile neutropenia and grade 4 thrombocytopenia after cycle 4 and one due to grade 3 peripheral neuropathy after cycle 4. There were a total of 6 DLT in the second stage of accrual: 1 grade 3 hepatic toxicity, 1 grade 4 thrombocytopenia, 1 grade 3 confusion, 1 grade 3 febrile neutropenia/grade 4 thrombocytopenia, 2 grade 3 peripheral neuropathy.

Toxicity results are shown in Table 4. Forty patients were evaluable for toxicity over six cycles. Thirty-one patients completed protocol treatment, defined as 6 or more cycles of dose dense therapy. A total of 12 DLT were observed in 40 patients (30%; 90% 2-sided CI 19.2% to 46.8%). Nine out of the 12 DLT and all of the grade 3/4 neurotoxicity and thrombocytopenia occurred at cycle 4 or later. The only DLT that occurred earlier than cycle 4 were: grade 3 dehydration, grade 3 non-neutropenic infection, and grade 3 SVT. There were 11 treatment related delays including: 5 grade 3/4 thrombocytopenia, 2 grade 1/2 thrombocytopenia, 2 grade 2 sensory neuropathy, 1 each grade 3 fatigue, grade 3 nausea/vomiting, and grade 3 hepatic toxicity. There were five paclitaxel dose reductions (three for neuropathy, one for AST/ALT elevation, one for thrombocytopenia) and four carboplatin dose reductions (all for thrombocytopenia). Nineteen patients required red blood cell transfusions (some patients required more than one) and one patient required platelet transfusion. Twelve patients (30%) had $\geq$ grade 2 neuropathy.

Efficacy results are shown in Table 5. Six patients were not assessable for response because they completed fewer than 4 cycles of treatment and went off study for reasons not involving progression. The reasons for not completing four or more cycles of treatment were: paclitaxel reaction (2), sudden death (1), gastric primary (1), fatigue (1), and SVT (1). Two patients were inevaluable for response because of normal pre-chemotherapy CA 125 levels and normal baseline CT scans. Of the 35 patients that were assessable for response, 19 had measurable disease and 16 were evaluable for CA 125 response. Of the 19 patients with measurable disease, six (31.6%) patients had a complete response, five (26.3%) patients had a partial response (overall RR 58%), seven (36.8%) patients had stable disease, and one (5.2%) patient had disease progression. Of the 16 patients evaluable for CA 125 response, 14 (87.5%) had a complete response, one (6.3%) had a partial response, and one (6.3%) had stable disease.

After 12 months of follow up, 67% of patients were progression free and 89% were alive. Three patients were not assessable for PFS and OS. Two of those three patients had paclitaxel hypersensitivity reactions and so did not complete one cycle of chemotherapy. The other patient was later found to have a gastric primary. Figure 1 shows the survival curves.

DISCUSSION

This feasibility trial of dose dense carboplatin/paclitaxel and pegfilgrastim demonstrated encouraging activity in patients with untreated advanced ovarian cancer. Seventy-two percent of patients completed six or more cycles of dose dense carboplatin/paclitaxel. However, based on the statistical design of the study, given the number of DLT (12 in 40 patients, 30%) this regimen was considered not feasible for further investigation without

modification. The study did not reach the targeted accrual of evaluable patients for the second stage since a sufficient number of DLT were observed to declare the regimen not feasible before study completion. Therefore, some bias in the estimate may exist but it is not expected to be severe (more than 92% of the intended accrual was obtained).

It is interesting to note when these DLT occurred. As previously stated, nine out of the 12 DLT and all of the grade 3/4 neurotoxicity and thrombocytopenia occurred at cycle 4 or later. Four of the DLT occurred at cycle 5 or later. Therefore, predominant toxicity from this regimen is cumulative. If the regimen was evaluated for DLT over the first four cycles, the regimen would have been declared feasible. This suggests that it may be a good preoperative regimen in patients who may be candidates for neoadjuvant therapy for three cycles. Using a regimen scheduled every two weeks could help patients get to the operating room faster. Vergote et al. have previously shown that treatment consisting of platinum-based neoadjuvant chemotherapy given every three weeks for three cycles followed by interval debulking surgery in patients with Stage IIIc or IV ovarian cancer, produces similar OS (30 months versus 29 months) and PFS (12 months in both arms) compared to standard primary debulking followed by chemotherapy but with less morbidity. [19]

Our results are similar in some ways to the earlier studies of weekly dose dense carboplatin/paclitaxel (Table 6). While comparing across studies is fraught with difficulties (particularly when the studies addressed varying patient populations- Table 6), there are several observations that can be made. The neutropenia in our study is lower than it is in the other trials likely due to the routine use of pegfilgrastim in our regimen. The thrombocytopenia in our study was similar to the other dose dense studies, except the Katsumata study where the rate was higher. [15] The higher rate of thrombocytopenia in the Katsumata study was likely due to the higher dose of carboplatin used. Neuropathy, however, occurred at a higher rate in our study than in most of the other studies. This may in part relate to a greater median number of cycles delivered in this untreated population as compared to previously treated patients. It is interesting to note that despite the fact that the other studies were in heavily pretreated patients (Table 6), our neuropathy was worse probably due to the dose and schedule of paclitaxel used in our study as compared to the weekly regimens.

In ovarian cancer, every two week therapy is not as advantageous as it seems in breast cancer. The neurotoxicity and thrombocytopenia render our dose dense regimen more problematic than in breast cancer studies. In the dose dense breast cancer study, paclitaxel was used as a sequential single agent and given for four cycles while six cycles were given in our study. [10] Also, when paclitaxel is added to platinum, it increases cumulative toxicity, especially neurotoxicity.

The role of dose dense therapy in ovarian cancer requires further study and the optimal dose and schedule have not yet been established. In GOG 9919, dose dense carboplatin combined with paclitaxel and pegfilgrastim was effective but based on the DLT is not feasible for six cycles. Given the neuropathy and thrombocytopenia, we do not recommend further investigation of this regimen without modification. However, consideration of this regimen in the preoperative setting may be appropriate. Incorporating dose dense therapy into intraperitoneal chemotherapy, neoadjuvant therapy, biologics and other new agents will be future challenges. The next GOG upfront trial will compare weekly carboplatin/paclitaxel to every three week therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Progression – Free Survival and Survival

Figure 1.
Kaplan-Meier Estimates of Progression Free Survival (PFS) and Overall Survival (OS)

Table 1

Previous Studies of Dose Dense Therapy in Previously Treated Ovarian Cancer

Author	Regimen	RR	CR	PFS
Havrilesky 2003 number= 29	P80+AUC2 d1,8,15 every 4 weeks	83%	55%	11.5 months
Rose 2005 number=28	P80 d1,8,15+AUC5 every 3 weeks	77%	58%	14 months
Cadron 2007 number=33	P90+AUC4 d1,8 every 3 weeks	66%	21%	9 months
Sharma 2009 number=23	P70+AUC3 d1,8,15 every 4 weeks	60%	0	8 months

Abbreviations: RR, response rate; CR, complete response; PFS, progression free survival; AUC, area under the curve; P, paclitaxel; d, day

Table 2

Demographics and Baseline Characteristics

Patient Demographics and Clinical Characteristics	Number of Patients (number=43)	% of Patients
Age, years		
Median	58	
Range	34–83	
Primary Site		
Ovary	38	88
Primary Peritoneal	2	5
Fallopian Tube	2	5
Other-Gastric	1 *	2 *
Stage		
III	37	86
IV	6	14
Surgical Procedure		
Staging/Debulking	41	95
Inoperable/Biopsy Only	2	5
Type of Debulking		
** Optimal	32	74
Suboptimal	11	26

* ineligible

** Optimal Debulking- After surgical resection, all cancer has been removed except for residual disease that measures less than 1cm in maximum tumor diameter.

Table 3

Number of Cycles Completed

Number of Cycles Completed	Number of Patients	% of Patients
0	2	5
1	1	2
2	2	5
3	1	2
4	4	9
5	2	5
6	25	58
7	0	0
8	6	14

Table 4

Grade 3 or 4 Adverse Events

	Grade (number=40)			
	3		4	
Adverse Event	No.	%	No.	%
Anemia	6	15	2	5
Thrombocytopenia	4	10	4	10
Neutropenia	6	15	1	2.5
Febrile Neutropenia	1	2.5	0	0
Infection	1	2.5	0	0
Neuropathy	3	7.5	1	2.5
Supraventricular Tachycardia	1	2.5	0	0
AST/ALT Elevation	1	2.5	0	0
Fatigue	1	2.5	0	0
Confusion	1	2.5	0	0
Dehydration	1	2.5	0	0

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; No., number

Table 5

Treatment Outcomes

Best Response	Measurable Patients (number=19)		Evaluable Patients (number=16)	
	No.	%	No.	%
Complete Response	6	31.6	14	87.5
Partial Response	5	26.3	1	6.3
Stable Disease	7	36.8	1	6.3
Progressive Disease	1	5.2	--	--

Abbreviations: No., number

Table 6

Studies of dose dense therapy in ovarian cancer (On-Line only)

Author	Regimen	Grade 3/4 neutropenia	Grade 3/4 thrombocytopenia	≥ Grade 2 neuropathy	Platinum Sensitivity/Line of Therapy
Havrilesky 2003 number=29	P80+AUC2 d1,8,15 every 4 weeks	32%	14%	0	Platinum sensitive & platinum resistant patients/Median number of 2 prior lines of therapy
Rose 2005 number=28	P80 d1,8,15 + AUC5 every 3 weeks	53%	18%	1 patient grade 2	Platinum sensitive/Average of 1 prior line of therapy
Cadron 2007 number=33	P90+AUC 4 d1,8 every 3 weeks	34%	25%	6%	Platinum sensitive & platinum resistant/Median number of 2 prior lines of therapy
Sharma 2009 number=23	P70+AUC 3 d1,8,15 every 4 weeks	29%	0	6%	Platinum resistant/Average of 3 prior lines of therapy
Katsumata 2009 number=312	P80 d1,8,15 + AUC6 every 3 weeks	92%	44%	24%	Platinum sensitive/First line therapy
Tiersten 9919 number=40	P175+AU C5 every 2 weeks	16%	18%	25%	Platinum sensitive/First line therapy

Abbreviations: AUC, area under the curve; P, paclitaxel; d, day